GGAGGGCAGCAAGGACGGCACCAAGGGAGCTACCCCATGGACAGGGCCCCACAGAGACACCACCGGACAT
CTCGGGAGCTGCTGGCTGCAAAGAAGACCCACACCTCACAAATTGAAGTGATCCCTTGCAAGATCTGTGG
GGACAAGTCATCTGGGATCCACTACGGGGTTATCACCTGTGAGGGGTGCAAGGGCTTCTTCCGCCGCAGC
CAGCAGTGTAATGTGGCCTACTCCTGCACGCGTCAGCAGAACTGCCCCATTGACCGAACCAGCCGCAACC
GATGCCAGCATTGCCGCCTGCAGAAGTGCCTGGCTCTGGGCATGTCCCGAGATGCTGTCAAGTTTGGCCG
AATGTCCAAGAAGCAGAGGGACAGTCTACATGCAGAAGTGCAGAAACAACTGCAACAGCAGCAGCAACAG
GAACAAGTGGCCAAGACTCCTCCAGCTGGGAGCCGCGGAGCAGACACACTTACATACACTTTAGGGCTCT
CAGATGGGCAGCTACCACTGGGCGCCTCACCTGACCTACCCGAGGCCTCTGCTTGTCCCCCTGGCCTCCT
GAGAGCCTCAGGCTCTGGCCCACCATATTCCAATACCTTGGCCAAAACAGAGGTCCAGGGGGCCTCCTGC
CACCTTGAGTATAGTCCAGAACGAGGCAAAGCTGAAGGCAGAGACAGCATCTATAGCACTGACGGCCAAC
TTACTCTTGGAAGATGTGGACTTCGTTTTGAGGAAACCAGGCATCCTGAACTTGGGGAACCAGAACAGGG
TCCAGACAGCCACTGCATTCCCAGTTTCTGCAGTGCCCCAGAGGTACCATATGCCTCTCTGACAGACATA
GAGTACCTGGTACAGAATGTCTGCAAGTCCTTCCGAGAGACATGCCAGCTGCGACTGGAGGACCTTCTAC
GGCAGCGCACCAACCTCTTTTTCACGGGAGGAGGTGACCAGCTACCAGAGGAAGTCAATGTGGGAGATGTG
GGAGCGCTGTGCCCACCACCTCACTGAGGCCATTCAGTATGTGGTGGAGTTTGCCAAGCGGCTTTCAGGC
TTCATGGAGCTCTGCCAGAATGACCAGATCATACTACTGACAGCAGGAGCAATGGAAGTCGTCCTAGTCA
GAATGTGCAGGGCCTACAATGCCAACAACCACACAGTCTTTTTTGAAGGCAAATACGGTGGTGTGGAGCT
GTTTCGAGCCTTGGGCTGCAGCGAGCTCATCAGCTCCATATTTGACTTTTCCCACTTCCTCAGCGCCCTG
TGTTTTTCTGAGGATGAGATTGCCCTCTACACGGCCCTGGTTCTCATCAATGCCAACCGTCCTGGGCTCC
AAGAGAAGAGGAGAGTGGAACATCTGCAATACAATTTGGAACTGGCTTTCCATCATCATCTCTGCAAGAC
TCATCGACAAGGCCTCCTAGCCAAGCTGCCACCCAAAGGAAAACTCCGGAGCCTGTGCAGCCAACATGTG
GAAAAGCTGCAGATCTTCCAGCACCTCCACCCCATCGTGGTCCAAGCCGCCTTCCCNCCACTCTATAAGG
AACTCTTCAGCACTGATGTTGAATCCCCTGAGGGGCTGTCAAAGTGATCTGGAGGAAGGACAACTTTCTA
TTTCCTTCAGCCCTCTGACCCGTCTCCCTGGACTCCCTTCACCCAGCCTTTCCCTTTCTGCACTCTATGA
AGGGTGGTATCCCTAGGAGTAAGCAAATCCTAAGACTGATTTTCTGCCCCTAGGCTTGCCTTGTAGGACA
ACAGCAGCAAGTGATGGAGAAAAGGCTTGTTATGTTTGATTTCCCATAAGTTCCACCCTGGCTTCTGGAA
GCTGTGGGGTAGATGGGATAGAGATAGGATGACCAAGTCAAATAAAAAACAGACTGACAATCAGCAGGGA
TAAATCCAGGTACCTGGGATAAGGAGAACTCAAATCTAGGCTTGAAAGCTAATAACAGTCCTTTCAATAC
CTCATTGTATTTCCCCATGGGTCCTCCTGGGGGGACATGGATCTAGCTCAGAGACTGGTGGCAAGCCCCC
AGAAGGACCTGTATATAATAAGAATATAGATTCCTG (SEQ ID NO:1)

MDRAPQRHHRTSRELLAAKKTHTSQIEVIPCKICGDKSSGIHYGVITCEGCKGFFRRSQQCNVAYS
CTRQQNCPIDRTSRNRCQHCRLQKCLALGMSRDAVKFGRMSKKQRDSLHAEVQKQLQQQQQQE
QVAKTPPAGSRGADTLTYTLGLSDGQLPLGASPDLPEASACPPGLLRASGSGPPYSNTLAKTEVQG
ASCHLEYSPERGKAEGRDSIYSTDGQLTLGRCGLRFEETRHPELGEPEQGPDSHCIPSFCSAPEVPY
ASLTDIEYLVQNVCKSFRETCQLRLEDLLRQRTNLFSREEVTSYQRKSMWEMWERCAHHLTEAIQ
YVVEFAKRLSGFMELCQNDQIILLTAGAMEVVLVRMCRAYNANNHTVFFEGKYGGVELFRALGC
SELISSIFDFSHFLSALCFSEDEIALYTALVLINANRPGLQEKRRVEHLQYNLELAFHHHLCKTHRQG
LLAKLPPKGKLRSLCSQHVEKLQIFQHLHPIVVQAAFPPLYKELFSTDVESPEGLSK (SEQ ID NO:2)

FIG. 1

underlined = deleted in targeting construct

green = sequence flanking Neo insert in targeting construct

```
GGAGGGCAGCAAGGACGGCACCAAGGGAGCTACCCCATGGACAGGGCCCCACAGAGACAC
CACCGGACATCTCGGGAGCTGCTGGCTGCAAAGAAGACCCACACCTCACAAATTGAAGTG
ATCCCTTGCAAGATCTGTGGGGACAAGTCATCTGGGATCCACTACGGGGTTATCACCTGT
GAGGGGTGCAAG[GGCTTCTTCCGCCGCAGCCAGCAGTGTAATGTGGCCTACTCCTGCACG
CGTCAGCAGAA]CTGCCCCATTGACCGAACCAGCCGCAACCGATGCCAGCATTGCCGCCTG
CAGAAGTGCCTGGCTCTGGGCATGTCCCGAGATGCTGTCAAGTTTGGCCGAATGTCCAAG
AAGCAGAGGGACAGTCTACATGCAGAAGTGCAGAAACAACTGCAACAGCAGCAGCAACAG
GAACAAGTGGCCAAGACTCCTCCAGCTGGGAGCCGCGGAGCAGACACACTTA[CATACACT
TTAGGGCTCTCAGATGGGCAGCTACCACTGGGCGCCTCACCTGACCTACCCGAGGCCTCT
GCTTGTCCCCCTGGCCTCCTGAGAGCCTCAGGCTCTGGCCCACCATATTCCAATACCTTG
GCCAAAACAGAGGTCCAGGGGGCCTCCTGCCACCTTGAGTATAGTCCAGAACGAGGCAAA
GCTGAAGGCAGAGACAGCATCTATAGCACTGACGGCCAACTTACTCTTGGAAGATGTGGA
CTTCGTTTTGAGGAAACCAGGCATCCTGAACTTGGGGAACCAGAACAGGGTCCAGACAGC
CACTGCATTCCCAGTTTCTGCAGTGCCCCAGAGGTACCATATGCCTCTCTGACAGACATA
G]AGTACCTGGTACAGAATGTCTGCAAGTCCTTCCGAGAGACATGCCAGCTGCGACTGGAG
GACCTTCTACGGCAGCGCACCAACCTCTTTTCACGGGAGGAGGTGACCAGCTACCAGAGG
AAGTCAATGTGGGAGATGTGGGAGCGCTGTGCCCACCACCTCACTGAGGCCATTCAGTAT
GTGGTGGAGTTTGCCAAGCGGCTTTCAGGCTTCATGGAGCTCTGCCAGAATGACCAGATC
ATACTACTGACAGCAGGAGCAATGGAAGTCGTCCTAGTCAGAATGTGCAGGGCCTACAAT
GCCAACAACCACACAGTCTTTTTTGAAGGCAAATACGGTGGTGTGGAGCTGTTTCGAGCC
TTGGGCTGCAGCGAGCTCATCAGCTCCATATTTGACTTTTCCCACTTCCTCAGCGCCCTG
TGTTTTTCTGAGGATGAGATTGCCCTCTACACGGCCCTGGTTCTCATCAATGCCAACCGT
CCTGGGCTCCAAGAGAAGAGGAGAGTGGAACATCTGCAATACAATTTGGAACTGGCTTTC
CATCATCATCTCTGCAAGACTCATCGACAAGGCCTCCTAGCCAAGCTGCCACCCAAAGGA
AAACTCCGGAGCCTGTGCAGCCAACATGTGGAAAAGCTGCAGATCTTCCAGCACCTCCAC
CCCATCGTGGTCCAAGCCGCCTTCCCNCCACTCTATAAGGAACTCTTCAGCACTGATGTT
GAATCCCCTGAGGGGCTGTCAAAGTGATCTGGAGGAAGGACAACTTTCTATTTCCTTCAG
CCCTCTGACCCGTCTCCCTGGACTCCCTTCACCCAGCCTTTCCCTTTCTGCACTCTATGA
AGGGTGGTATCCCTAGGAGTAAGCAAATCCTAAGACTGATTTTCTGCCCCTAGGCTTGCC
TTGTAGGACAACAGCAGCAAGTGATGGAGAAAAGGCTTGTTATGTTTGATTTCCCATAAG
TTCCACCCTGGCTTCTGGAAGCTGTGGGGTAGATGGGATAGAGATAGGATGACCAAGTCA
AATAAAAAACAGACTGACAATCAGCAGGGATAAATCCAGGTACCTGGGATAAGGAGAACT
CAAATCTAGGCTTGAAAGCTAATAACAGTCCTTTCAATACCTCATTGTATTTCCCCATGG
GTCCTCCTGGGGGGACATGGATCTAGCTCAGAGACTGGTGGCAAGCCCCCAGAAGGACCT
GTATATAATAAGAATATAGATTCCTG (SEQ ID NO:1)
```

FIG. 2A
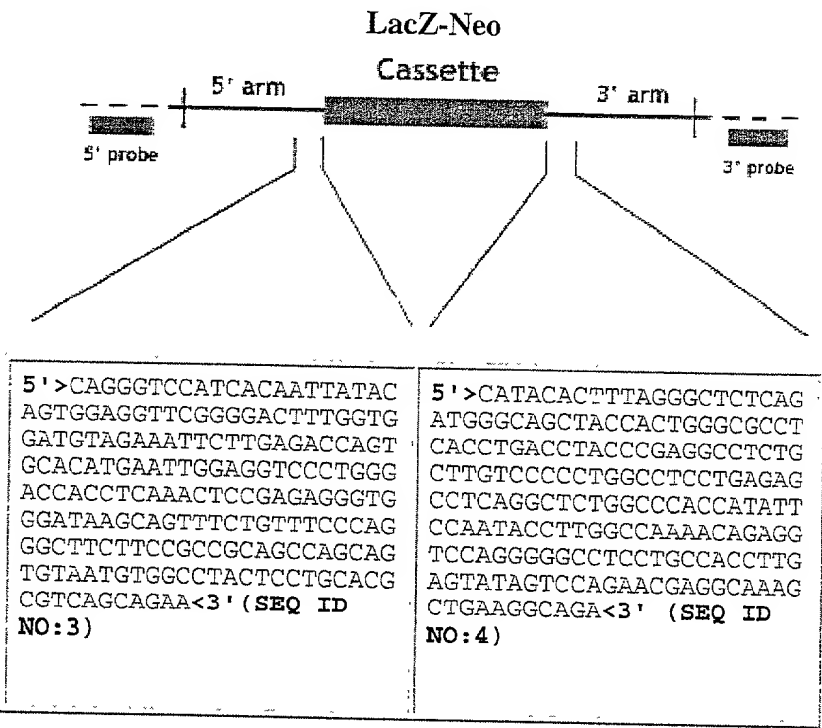
Gene Sequence
Structure *

252 bp   Sequence Deleted   472 bp

Size of full-length
cDNA: 2066 bp

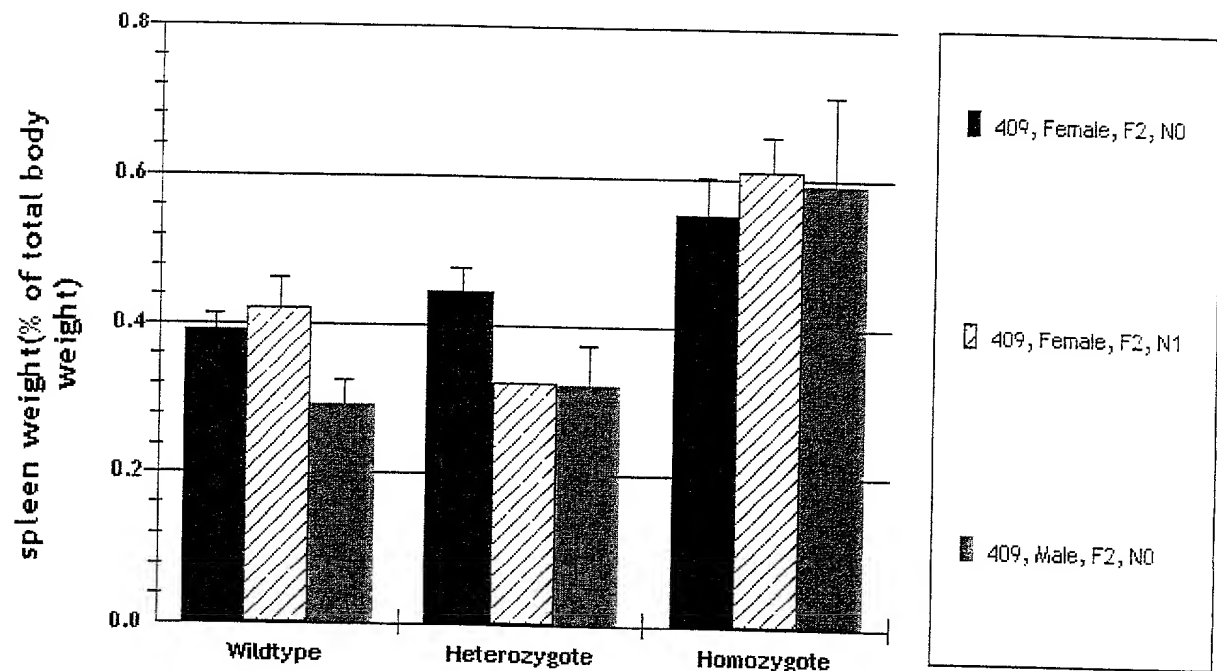Targeting Vector* (genomic sequence)

Construct Number: 651

LacZ-Neo
Cassette

5' arm   3' arm

5' probe   3' probe

Arm Length:
5': 1.6 kb
3': 2.5 kb

——— Targeting Vector
– – – – Endogenous Locus

*Not drawn to scale

```
5'>CAGGGTCCATCACAATTATAC
AGTGGAGGTTCGGGGACTTTGGTG
GATGTAGAAATTCTTGAGACCAGT
GCACATGAATTGGAGGTCCCTGGG
ACCACCTCAAACTCCGAGAGGGTG
GGATAAGCAGTTTCTGTTTCCCAG
GGCTTCTTCCGCCGCAGCCAGCAG
TGTAATGTGGCCTACTCCTGCACG
CGTCAGCAGAA<3'(SEQ ID
NO:3)
```

```
5'>CATACACTTTAGGGCTCTCAG
ATGGGCAGCTACCACTGGGCGCCT
CACCTGACCTACCCGAGGCCTCTG
CTTGTCCCCCTGGCCTCCTGAGAG
CCTCAGGCTCTGGCCCACCATATT
CCAATACCTTGGCCAAAACAGAGG
TCCAGGGGGCCTCCTGCCACCTTG
AGTATAGTCCAGAACGAGGCAAAG
CTGAAGGCAGA<3' (SEQ ID
NO:4)
```

FIG. 2B

necropsy - spleen weight/body weight

FIG. 3

necropsy - liver weight/body weight
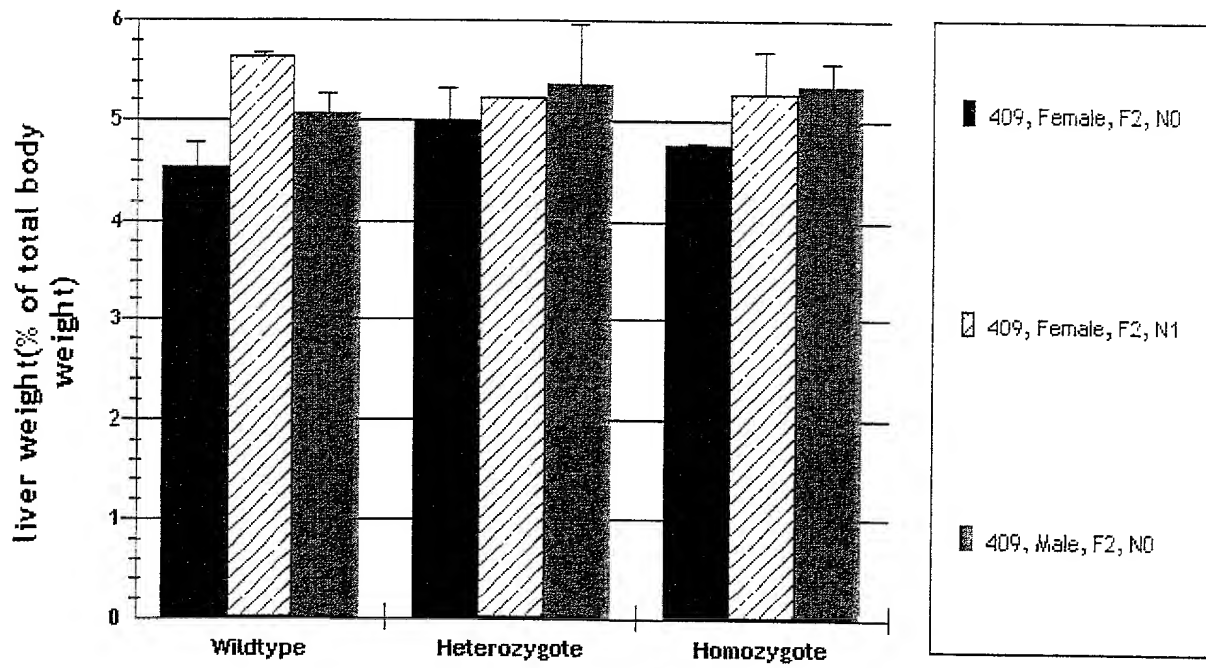
FIG. 4

necropsy - kidney weight/body weight

Legend:
- 409, Female, F2, N0
- 409, Female, F2, N1
- 409, Male, F2, N0

X-axis: Wildtype, Heterozygote, Homozygote

Y-axis: kidney weight(% of total body weight)
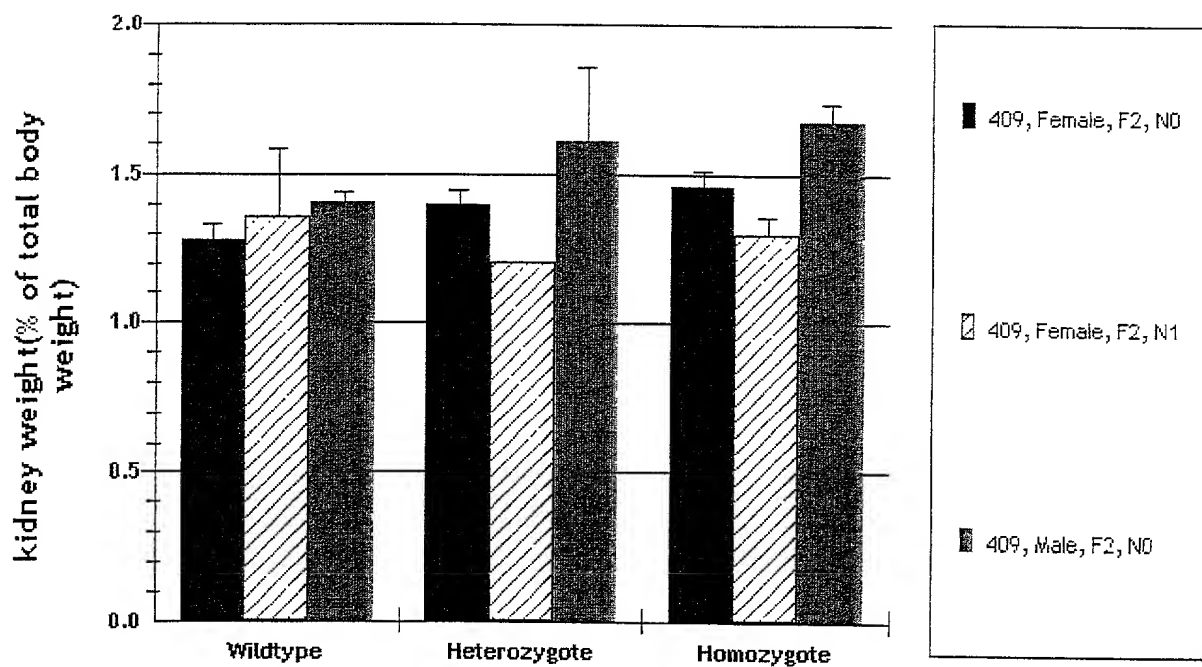
FIG. 5

necropsy - thymus weight/body weight

FIG. 6